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REMARKS

Rejections of Claims and Traversal Thereof

In the September 15, 2006 Office Action,

claims 1 and 74 were rejected under U.S.C. §112, second paragraph; and

claims 1-3, 6-9, 11, 13-16, 24, and 73-85 were rejected under U.S.C. §112, first paragraph.

Applicants traverse these rejections and submit that all claims, as now amended, meet the requirements of U.S.C. §112, first paragraph and second paragraph.

Rejection under U.S.C. §112, second paragraph

Claims 1 and 74 have been rewritten to recite that "the modified sequence has at least 95% identity to the full length reference sequence or truncated sequence" with support for such an amendment located on page 22 of the application. Applicants submit that the amendment to the claims obviates the rejection and request the withdrawal of the rejection under U.S.C. §112, second paragraph.

Rejection under U.S.C. §112, first paragraph

According to the Office, claims 1-3, 6-9, 11, 13-16, 24, and 73-85 contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is mostly connected, to make and/or use the invention.

Claim 1 of the present invention, as amended herein, reads as follows:

> 1. A chimeric polypeptide comprising: a virus coat polypeptide sequence, a viral cell surface receptor polypeptide and an amino acid sequence spacer, wherein the amino acid sequence of the chimeric polypeptide is a full length reference sequence, a truncated sequence or a modified sequence, wherein the modified sequence has at least 95% identity to the full length reference sequence or truncated sequence with similar functionality thereof, wherein the chimeric polypeptide has the functionality

> of forming an intramolecular interacting complex between the virus coat polypeptide and viral cell surface receptor, wherein the virus is an immunodeficiency virus selected from the group consisting of retroviruses HIV, SIV, FIV, and FeLV, wherein the viral cell surface receptor polypeptide sequence comprises amino acid residues of the region having binding–affinity for the virus coat polypeptide sequence, and the amino acid sequence spacer is linked to both the virus coat polypeptide sequence and the viral cell surface receptor polypeptide sequence and positioned therebetween to form a single chain polypeptide of peptidic bonds, wherein the spacer consists of an amino acid sequence of sufficient length to allow the single chain polypeptide to fold thereby permitting the virus coat polypeptide sequence and the viral cell surface receptor polypeptide sequence to form the intramolecular interacting complex.

The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. See *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 109 S.Ct. 1954 (1989).

In the September 15, 2006 Office Action, the Office states that the "the specification provides no exemplification of a chimeric polypeptide, which amino acid sequence is truncated or modified, forming an intramolecular complex and interacting with or blocking a cellular co-receptor that is utilized by a virus for infection." The Office then goes on to state that:

> "It is largely unpredictable how the truncation and modification of the chimeric polypeptide will affect the functionality of the chimera to form an intramolecular complex and to interact with or block a cellular co-receptor, which virus utilizes for infection."

The issue raised by the Office seems to relate to whether one skilled in the art could make and use the claimed invention without undue experimentation. Applicants submit that the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co., v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeal summarized the point well when it stated:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the

> direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." *Ex parte Jackson*, 217 USPQ 804, 807 (1982).

Here, all the Office has established is that some experimentation would be required to make and use other embodiments of the claimed invention. However, the specification provides ample guidance for testing variant proteins that meet the criteria set forth in the presently claimed invention. It should be noted that claim 1 defines parameters that enable broader protein claims because the claim recites functional language that clearly defines the functionality of the chimeric polypeptides, including truncated and modified forms and their activity. According to the Court in *In re Marks*, 12 USPQ2d 1904 (BPAI 1989) with the addition of functional language, one skilled in the art would be able to determine in a routine fashion, without undue experimentation whether the chimeric polypeptide forms an intramolecular complex.

The biological activity, that being, the ability to form an interacting intramolecular complex can be very easily determined by one skilled in the art with the use of routine assays, and the specification provides guidance as set forth in Examples II, IV and VII (according to the parameters set forth by the *Jackson* and *Atlas* Court). Example III shows the results of the truncated chimeric and the interaction with specific cell antibodies that are only bindable when the chimeric has a specific conformation. Specifically, as discussed at page 44 of the specification, two of the antibodies, 17b and 48d, bind within the co-receptor attachment site that is induced by CD4 binding (N. Sullivan et al., J. Virol., 72: 4694-703 (1998); A. Trkola et al., Nature, 384: 184-6 (1996); L. Wu et al., Nature, 384: 179-183 (1996)). As shown in FIG. 5B of the specification, the level of 17b and 48d reactivity with TcSC was equivalent to what was observed with FLSC analyzed in parallel. This data indicates an interaction between cell receptor sequences and the virus coat sequences present within FLSC and TcSC molecules.

Example IV of the present specification describes data demonstrating the binding of gp120-CD4 chimeric molecules to CCR5 expressing cells. Notably, the complexes would not exhibit such binding if they did not form the necessary intramolecular complex as recited in claim 1.

The specification gives guidance for binding assays. For example, to evaluate the ability of the single-chain complexes to bind a co-receptor, purified single-chain gp120-CD4 chimeric polypeptides

were allowed to interact with cells that express either CCR5 or CXCR4. For the binding, the purified single-chain preparation was allowed to interact with L1.2 cells that express CCR5 (L. Wu et al., Nature, 384: 179-183 (1996); L. Wu et al., J. Exp. As shown in FIG. 6 of the specification, both single chain complexes (FLSC and TcSC) bound to the CCR5-expressing, but not CXCR4-expressing, L1.2 cells. Thus, gpl20-CD4 chimeric polypeptide presents functional co-receptor binding site (s) for CCR5, as expected for a molecule containing a macrophage tropic gpl20.

To demonstrate that single-chain gpl20-CD4 is binding to CCR5 through its co- receptor binding site, competition binding studies with 17b and 48d antibodies, which have been shown to interact with the co-receptor binding site of gpl20 and prevent gpl20/sCD4 complexes from interacting with co-receptor expressing cells, were performed. As shown in FIG. 7, 17b and 48d antibodies strongly inhibited the binding of both the FLSC and TcSC single-chain complexes to the cells.

Example VII describes data demonstrating that mutation of the furin cleavage site improves the stability of the FLSC complex. Notably, the specification clearly states that cleavage of the FLSC at the natural furin site would be consistent with the behavior of the FLSC fragments, as it would have minimal impact on the structures of the gpl20 and CD4 moieties and their capacity to interact. The results in FIG. 13 show that mutation of the furin cleavage site prevents the V1V2 found on the FLSC R/T from dissociating as readily as the cleaved FLSC, thus improving its stability of the FLSC R/T complex. Notably, one skilled in the art can easily determine the ability of the modified sequence to form the intramolecular complex by using the testing methods of Example III by determining the level of binding of the 17b antibody

Thus, the breath of the claims is not broader than that described in the specification and the quantity of experimentation to practice the full scope of the claims does not require undue experimentation. The specification provides guidance regarding how to make and use a truncated or modified chimeric polypeptide. Clearly, the level of skill in this field is very high and one skilled in the art is very aware of these routine testing assays. As such, information known by one skilled in the art will provide ample assistance in practicing the claimed invention, and as such, known prior art contributes significantly to the enabling scope of the disclosure.

The Office has provided several references to show the unpredictability of truncation and modification of the chimeric polypeptide. However, it is very important for the Office to recognize that the cited references relate to modeling methods, using computational systems, to determine protein tertiary structure from an available linear sequence. However, applicants have clearly stated that the functionality of the truncated and modified chimerics relates to having the ability to form the intramolecular complex. This functionality can be easily determined by routine assays and as such, using computational methods to determine the structure is not necessary or required. Applicants insist the presently claimed invention must not be viewed in a vacuum but instead in the context of what was known to those skilled in the art at the time of filing and that set forth in the specification.

According to the Office, the Wand factors must be considered including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Reviewing these factors, applicants insist that the factors, in the present situation, weigh toward undue experimentation. The present application provides multiple working examples verifying the intramolecular formation and provides testing regimes to test the formation of such complexes. These tests are clearly defined in the specification and easily conducted. A simple test with the 17b monoclonal antibody will provide sufficient information regarding the formation of an intramolecular complex by either a truncated or a modified sequence. Thus, one skilled in the art having an undergraduate degree in biology or chemistry could easily carry out the routine assays described in the present specification and taught in most undergraduate Molecular Biology courses. Further, the generation of an amino acid sequence, either by cell expression or by synthesis, is no longer an unpredictable art, and as such, the generation of such a sequence is easy conducted with subsequent testing relating to formation of an intramolecular complex. Applicants insist that the specification supports the breadth of the claims.

Applicant submits that the instant application provides sufficient and enabling information for a person of ordinary skill in the art to practice applicants' invention and respectfully requests the withdrawal of all rejections under §112, first paragraph.

Rejoining of Method Claims

Applicants are requesting that all method and use claims that are currently withdrawn be rejoined and examined according to the guidelines set forth in Section 821.04 of the MPEP. The Office has agreed that claims 34, 35, 37, 38, 40 and 41-45 will be considered for rejoining.

However, the Office believes that claims 46, 49-57, 60-63 and 65 cannot be rejoined because product claims 1-3, 6-9, 11, 13-16, 24 and 73-85 "do not encompass various types of agents that are used in process claims 46, 49-57, 60-63 and 65." According to Section 821.04 of the MPEP, "if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims which either depend from or **include all the limitations of the allowable product will be rejoined.**" (emphasis added) Notably, the wording of this section of the MPEP does not say that the product claim has to encompass various types of agents used in the process claims but instead states that the process claim includes all the limitations of the product claim There is no restriction that the process claim that prevent the process claim from including and addition limitation, such as the testing agent. As such, applicants request that all process claims be rejoined.

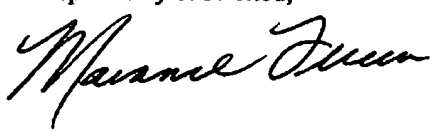
Fees Payable

Applicants have added one additional new claim but have cancelled numerous claims during the prosecution of this application, and as such, no fee is due. In the event a fee is found due, the Commissioner is authorized to charge such amount due to Deposit Account No. 13-4365.

Conclusion

Applicant has satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Boesen reconsider the patentability of all pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Boesen is requested to contact the undersigned attorney at (919) 286-8089 to resolve same.

Respectfully submitted,



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